Upsetting the balance: lipoprotein receptors in the CNS

Helen Dell, BMN News

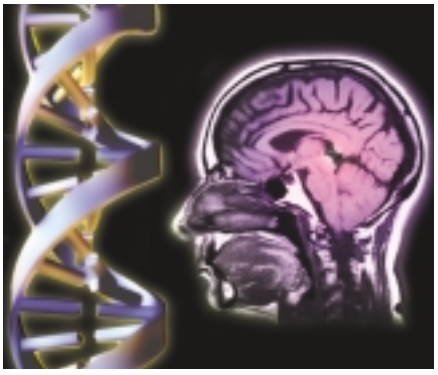
An imbalance between two roles of lipoprotein receptors - cholesterol transport and neuronal signalling in the CNS - could help explain the link between apolipoprotein E4 (ApoE4) and Alzheimer's disease (AD), say neuroscientists.

ApoE4 and Alzheimer's disease

ApoE4 predisposes carriers to late-onset AD, explains Joachim Herz, Professor of Biophysics and Molecular Genetics at the University of Texas Southwestern Medical Center (http://www.swmed.edu). 'What we were wondering was whether the receptors that ApoE binds to might also be involved,' he said.

The receptors that ApoE binds are highly conserved – they appear in very primitive multi-cellular organisms, like the nematode worm, which diverged from the human lineage about 800 million years ago. 'These receptors must have had completely different functions, because they are already present in the worm in virtually the modern form, and there was no ApoE around at that time,' noted Herz.

ApoE arose during mammalian evolution, which suggests it must have evolved to fit a pre-existing receptor, and the receptors to which it binds must have had another, more primordial function. 'We think that these primordial roles of these receptors are important in tissue organization and transmitting signals between cells in various tissues, for instance in the vascular walls...or in the CNS where it is regulating the development of the neocortex and the cortical layering,' said Herz.



A new hypothesis

'Our hypothesis is that apolipoprotein E, because it evolved onto a pre-existing receptor system, might actually interfere with these original functions – for instance, in regulating neuronal migration or, as we are now showing, in regulating synaptic neurotransmission itself.'

Herz's team examined the three different apolipoprotein E isoforms, ApoE2, -E3 and -E4. They found that the rare E2 isoform binds very poorly to the receptors because it is missing a positive charge in the region that interacts with the receptors. In the same region, ApoE4 has one more positive charge than the more-common E3 and two more positive charges than E2, so ApoE4 can bind very well to the receptors and the cell surface. Also, the lipoprotein particles around which ApoE4 assembles tend to be larger than the ApoE3 particles.

'All in all, this makes ApoE4, in our minds, a better competitor for ligand binding to the receptors than E3 or E2, and it will be interfering more with the primordial function of the receptor,' concluded Herz.

The enhanced binding of ApoE4 to these receptors would then 'dampen' their primordial physiological function. 'So instead of having a receptor system that is active at 100%, the system might only be active at 80% or 90%. And by dampening a pro-survival, pro-neuronal function, you might actually gain the modifier effect that you see in late-onset Alzheimer's,' suggested Herz.

Ligand competition

'It's a very attractive idea,' said Jonathan Cooper, of the Fred Hutchinson Cancer Center in Seattle, Washington. 'There is some evidence that it might be true, but it'll need a lot more work to find out.'

The receptors have generally been thought of as 'just bringing various nutrients into the cell,' said Cooper. 'That was the historical view until a few years ago, and now there is evidence that they might be signalling receptors as well. But how much competition there is between the different ligands has yet to be shown,' he said.

Herz and his colleagues have found a ligand called reelin that is present in the CNS and binds to two apolipoprotein receptors, ApoER2 and the VLDL receptor. Reelin regulates neuronal migration and positioning in the brain during embryonic development, but is also expressed in the adult brain.

'This molecule very potently enhances synaptic transmission, and the strengthening of synaptic contacts between neurons, which is commonly thought to be one of the processes which is underlying memory and the

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maintenance of synapses,' said Herz. The synaptic loss is closely associated with AD and dementia, therefore, he believes that the interference of this process by ApoE4 might be involved in late-onset AD.

Future directions

But he suspects that the lipoprotein receptors will turn out to have other ligands as well. 'There are seven members of this gene family of receptors and all of them are expressed on neurons at some point during development, either throughout the brain or in specialized subsets,' he noted. 'We have identified a specific ligand, reelin for two of them, which means that the others most likely will have functional ligands which we simply do not know about.'

His goal is to identify them. 'We have a very strong lead on one of them,' he said. 'We are using mutants in which we have made very specific mutations in the receptors, which allows us to assess their role in the synapse. And from that we now have much more detailed information of how in the synapse ApoE receptors function in modulating neurotransmission.'

Cooper is excited by the prospect of a new ligand. 'If there is another compound out there which binds to these receptors and which alters neurotransmission, then people would certainly want to know about it,' he said. 'Sounds like we have to stay tuned.'

The work was presented at the 53rd annual meeting of the *American Society of Human Genetics* 4–8 November 2003 (http://www.ashg.org).

Single target's broad potential

Caroline Cross, BMN News

A novel treatment for flu that targets a marker expressed on recently activated T cells could be used to treat a host of immune mediated diseases, report UK researchers.

Excessive immune response

When mice infected with influenza A are treated with a protein that targets OX40, a costimulatory molecule expressed on recently activated T cells, the animals' flu symptoms disappear.

'In the lung you tend to see an immune response that far exceeds what is needed to clear the pathogen,' said team leader Tracy Hussell at Imperial College London, UK (http://www.ic.ac.uk), whose latest data are published in the *Journal of Experimental Medicine* [1]. It is this excessive immune response that causes symptoms such as coughing and wheezing.

Unlike other anti-inflammatory treatments, including corticosteroids that affect all T cells, the OX40 treatment only inhibits cells recently

activated with antigen. 'It specifically dampens down those cells that are responding at that time,' she said. If treatment is stopped while some cells remain in the lung, sufficient numbers enter the T cell memory pool to allow cellular immunity to develop.

Another advantage of the treatment is that it is not specific for a particular pathogen and so can be used to treat a range of inflammatory disorders.

Immunotherapy target

Andrew Weinberg, a researcher at the Providence Portland Medical Center in Oregon, USA (http://www.phsor.org), has shown that in animal models of autoimmunity, such as the mouse model of multiple sclerosis, so-called experimental autoimmune encephalomyelitis (EAE), downregulation of OX40 signalling blocks the initial waves of inflammation.

'We have shown that OX40 positive T cells are the autoantibody-specific T cells within the inflammatory lesions of EAE,' he said. Blocking OX40 signalling, or deleting OX40 positive cells, reduces the symptoms without affecting the rest of the T cell repertoire, he says.

And the versatility of this molecule as a target for immunotherapy does not stop with downregulation. Upregulating OX40 signalling can enhance desirable

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